Effects of flow and diffusion on blood coagulation in platelet poor plasma

A two-way coupling between hemodynamics and biochemistry

Diana Magnabosco[1,2]✉, Henk van Ooijen[1]✉, Bart Bakker[1], Rene van den Ham[1], Luca Formaggia[2]

1. Philips Research, Molecular Diagnostic Department, Eindhoven, Netherlands
2. Politecnico di Milano, Mathematical Department, Milan, Italy

✉ diana.magnabosco@mail.polimi.it, henk.van.ooijen@philips.com

Biological background

Enzyme reactions, blood flow and diffusion in human vasculature play interacting and fundamental roles in blood coagulation. In this complex mechanism, the balance between blood and clot is a delicate equilibrium between fluid and solid state, whose tight regulation is vital to avoid pathologies such as bleeding and thrombosis.

Secondary hemostasis in platelet poor plasma in large veins (Figure 1):

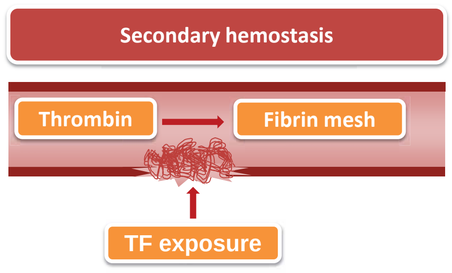
- Tissue factor (TF) exposed to blood after injury
- Coagulation network: cascade of different consecutively activating protein reactions with feedback loops (red)
- Thrombin (fIIa) is ultimately activated from prothrombin (fII)
- Fibrin (Fbn) is formed from fibrinogen (Fbg) and it polymerizes into insoluble polymers
- Activation processes are opposed by inhibitors (green)

Study of the impact of:

- Tissue factor initial concentration (TF_0)
- Wound size (L_w)
- Shear rate (γ)
- Diffusion (D)

Output parameters

- Thrombogram (lag time (t_{lag}), time to peak (t_{max}), maximum concentration (C_{max}) of thrombin)
- TGD (total amount of generated thrombin on the domain)
- Time to clot (t_{clot}) and clot size (A_{clot})
- Wound-Clot: normalized distance



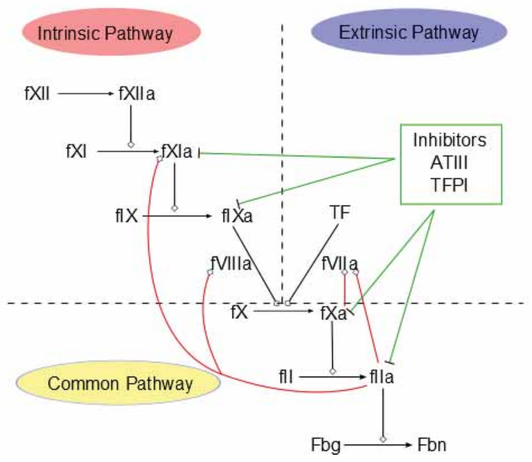


Figure 1: Coagulation network with activation of proteins, positive feedback loops (red) and inhibitors (green).

Mathematical and numerical methods

Coagulation network

- Plasma species in Ω, t>0

$$\frac{\partial \boldsymbol{c_p}(\boldsymbol{x},t)}{\partial t} - \mathrm{D}\nabla^2 \boldsymbol{c}_p(\boldsymbol{x},t) + \boldsymbol{u}(\boldsymbol{x},t)\cdot\nabla \boldsymbol{c_p}(\boldsymbol{x},t) = R_p(\boldsymbol{c}(\boldsymbol{x},t))$$

- Membrane species on Γ_{down}, t>0

$$\frac{\partial \boldsymbol{c_m}(x,t)}{\partial t} = R_m(\boldsymbol{c}(\boldsymbol{x},t))$$

- Coupling by boundary conditions on Γ_{down}, t>0

$$-\boldsymbol{n}\cdot D\nabla \boldsymbol{c_{pm}}(\boldsymbol{x},t) = R_{pm}(\boldsymbol{c}(\boldsymbol{x},t))$$

Linear finite elements method with streamline and crosswind numerical diffusion

46 PDEs for plasma species
11 ODEs on the wall for membrane species
1 ODE in the domain for fibrin

→ Transport of dilutes species interface
Boundary ODEs and DAEs interface
Domain ODEs and DAEs interface

Blood flow

- Modified Navier-Stokes equations in Ω, t>0

$$\rho\frac{\partial \boldsymbol{u}}{\partial t} + \rho\boldsymbol{u}\cdot\boldsymbol{\nabla u} = \boldsymbol{\nabla}\cdot[-p\boldsymbol{I} + \mu(\boldsymbol{x},t)(\boldsymbol{\nabla u} + \boldsymbol{\nabla}^T\boldsymbol{u})]$$

$$\boldsymbol{\nabla}\cdot\boldsymbol{u} = \boldsymbol{0}$$

- Viscosity depending on fibrin (threshold [Fbn]*)

$$\mu(\boldsymbol{x},t) = \mu([\mathrm{Fbn}]) = \begin{cases}\mu_{blood} & \text{if } [\mathrm{Fbn}] < [\mathrm{Fbn}]^* \\ \mu_{clot} & \text{if } [\mathrm{Fbn}] \geq [\mathrm{Fbn}]^*\end{cases}$$

P1+P1 with streamline and crosswind numerical diffusion

→ Laminar flow interface

Non-linear system: Newton method
Linear system: MUMPS
Time integration: BDF
Mesh: Finer near the wound where gradients are relevant
Tolerances: $\epsilon_{rel}=10^{-3}$ $\epsilon_{abs}=10^{-7}$

Parameters			
L_x	1000 µm	[Fbn]*	600 nM
L_y	200 µm	TF_0	90 fmol/m²
L_w	L_x/32	μ_{blood}	0.0035 kg/ms
D	$5\cdot10^{-11}$ m²/s	μ_{clot}	1 kg/ms
γ	1 1/s	ρ	1000 kg/m³

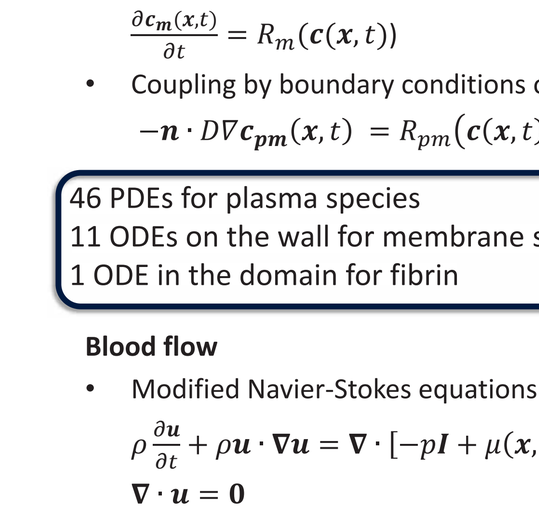


Figure 2: Shape of the viscosity function.

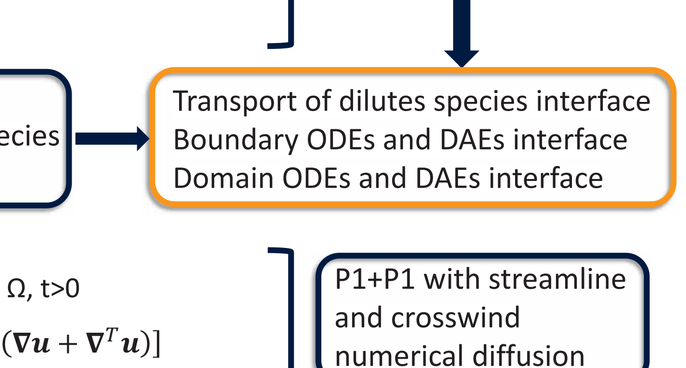
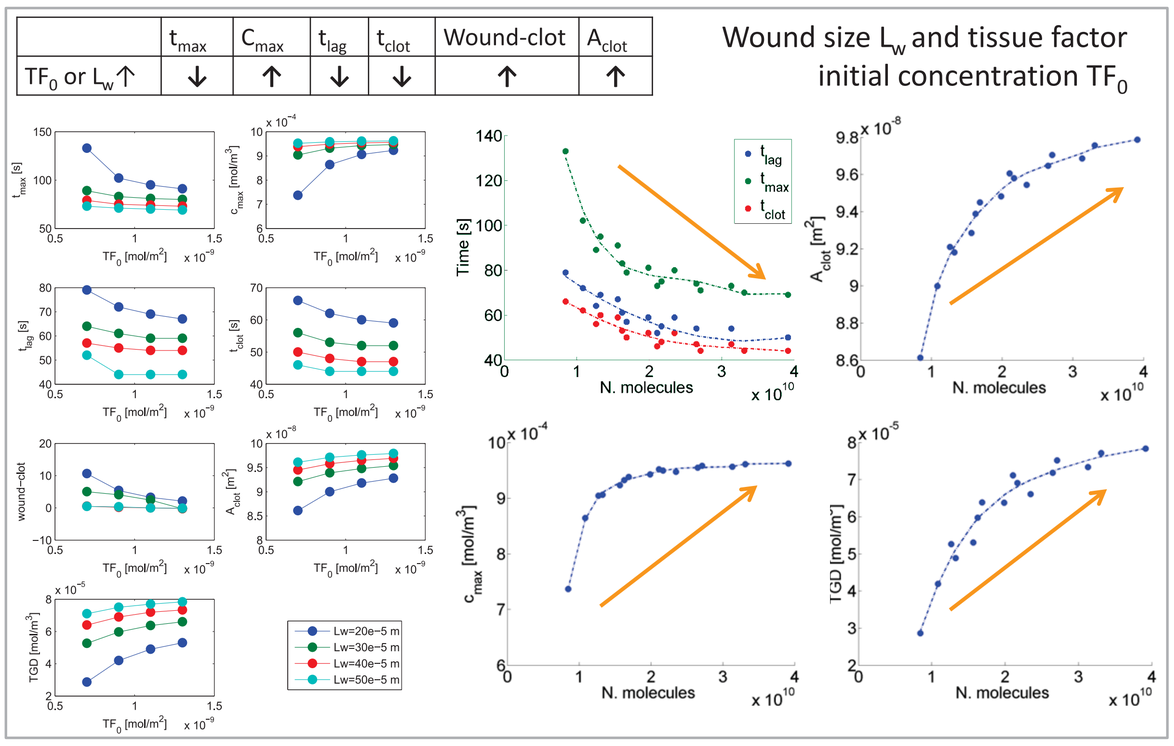


Figure 3: Geometry, boundary conditions and clot formation.

Results

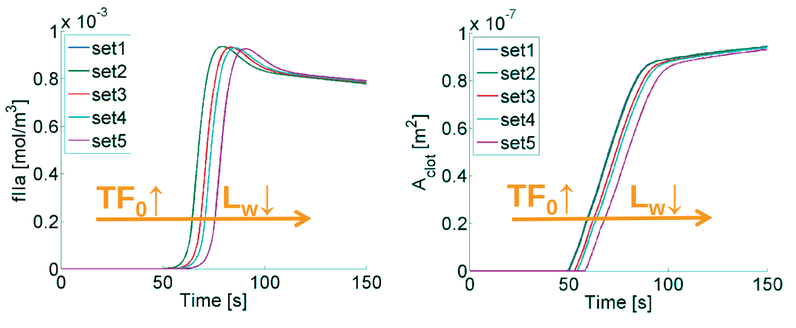
	t_{max}	C_{max}	t_{lag}	t_{clot}	Wound-clot	A_{clot}
TF_0 or L_w↑	↓	↑	↓	↓	↑	↑

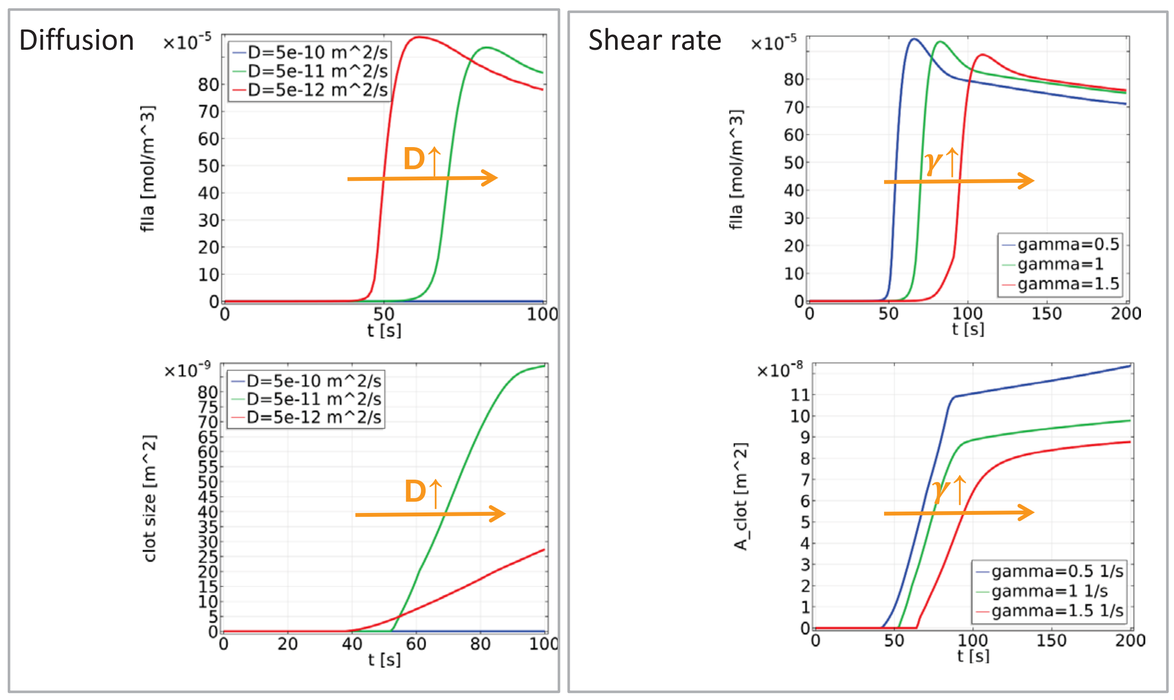
Wound size L_w and tissue factor initial concentration TF_0



Constant number of molucules of tissue factor on the wound

Set	TF_0 [fmol/cm²]	L_w [µm]
1	67.5	40
2	70	38.6
3	90	30
4	110	24.5
5	135	20





Conclusions

- Increasing TF_0 or L_w results in the thrombin burst being stronger and earlier, hence leading to the formation of an early and bigger clot.
- Output parameters are more sensitive to variation in L_w than TF_0, while keeping the total number of TF molecules fixed. Blood flow in combination with diffusion plays a pivotal role since the inactivated zymogens in the fluid are in contact with the same number of molecules, but stretched over a larger injury site, meaning a larger contact time/region.
- Flow and diffusion have a limiting role on the mechanism. If their values are bigger, the activation is less intense and delayed. The clot is formed later, farther from the wound and is smaller. The incoming inactive species brought by the flow are not enough to balance the removal of the active ones and as a result the balance between the pro-coagulant and anticoagulant effects of increased flow and diffusion tips in favour of the anticoagulant effect.

References

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